REMARKS

1. Amendments to the Claims

Claim 2 is herein amended per the Examiner's suggestion. Support for this amendment is found in the specification at page 16, line 1. Claims 1, 4, 6, 7, 12, 14, and 19 have been amended to be consistent with claim 2. No new matter is added.

2. Claim Objections

The Examiner objects to claim 2 for reciting "a partial peptide of a protein." Applicants have amended the claim, thereby obviating the objection. Applicants request that it be withdrawn.

Applicants submit that the present invention is patentable over the prior art of record. The favorable actions of withdrawal of the standing rejections and allowance of the pending claims are requested. Applicants earnestly request entry of the claim amendments, as they merely overcome a claim objection and do not raise a new issue.

3. Claim Rejections under 35 U.S.C. § 103

The Examiner rejects claims 2, 4, 6, 7, 19, 20, 25, and 26 under 35 U.S.C. § 103 as being unpatentable over Konya in view of Boeckle and Kubo. Applicants respectfully traverse.

a. One of skill would not have a reasonable expectation that PBF, of human origin, was immunogenic.

Applicants emphasize again that one of skill in the art would not have found the present invention obvious because the HPV8-E2 protein is not equivalent to SEQ ID NO: 2 of the present invention.

Boeckle discloses that PBF was identified as a human cellular factor that recognizes and binds to the *E2 binding site* of human papillomavirus type 8 gene. Boeckle *does not* disclose the HPV8-E2 protein. Also, although papillomavirus plays an important role in the onset of cancer, Boeckle is silent about the application of PBF or its epitope peptides in an effective cancer antigen vaccine.

HPV8-E2 protein is a viral protein derived from papillomavirus and regulates viral transcription. PBF **is derived from a human (i.e., the host of the virus)** that binds to one of the HPV8-E2 binding sites, P2 on the HPV8 gene.

Because PBF is a **human protein**, there is no expectation that it would be immunogenic.

Applicants further point out that the very definition of a "tumor antigen peptide" is a partial peptide or peptide fragment derived from protein expressed in a tumor cell. (See attached, Boon, Scientific American, March, (1993) pages 32-39). Neither Konya nor Boeckle suggest that PBF is expressed in a tumor cell. Applicants determined that PBF is a tumor antigen, as shown in Example 1 of the Specification by establishing an osteosarcoma cell line, a CTL cell line, and screening an enormous number of proteins derived from the osteosarcoma cell line against the CTL cell line.

Thus, a peptide, which is not known to be derived from a tumor cell, that is a human peptide, would not have been an obvious choice.

Applicants respectfully request that the rejection be withdrawn.

b. One of skill would not substitute PBF for HPV8-E2 because the two do not share a common structure.

When HPV8-E2 protein binds to a E2 binding site, P2 on the HPV8 gene, it causes repression of the transcription of said gene. PBF binds to the E2 binding site P2. **But PBF does not share homology with HPV8-E2 protein.** The Examiner's assertion is tantamount to: "if two proteins bind the same receptor, a vaccine made from one protein must be obvious in view of the disclosure of the other."

The sequence alignment below shows that the two proteins do not share any sequence homology.

The Sequence of HPV8-E2 was not disclosed in Boeckle, but it was known at the time of filing. *See* Stubenrauch and Pfister, J. Virol. 1994 68(11) 6959-66 cited in Boeckle (see page 17). On page 6960 of Stubenrauch, in the second paragraph of "Materials and Methods", it is disclosed that the whole E2 open reading frame of HPV8 is nucleotides 2682 to 4222. Based on this information and the known HPV8 complete genome available from GenBank accession No.

M12737 one of skill would have known the two sequences had very little, if any, sequence homology.

Applicants provide an alignment between the **HPV8-E2** protein amino acids 2682-4222 against the **PBF** sequence, SEQ ID NO: 2, which is deposited as Gen Bank Accession NO. AF263928. (Attached Sheet). This alignment shows that there is no or extremely low sequence homology between the two proteins. Accordingly, one of skill in view of Konya, Boeckle and Kubo, would not have found the presently claimed peptides for a cancer vaccine obvious, because one of skill 1) would not think that the peptides were immunogenic, and 2) there is no sequence homology (similarity) between the two sequences.

c. *The disclosure of Konya does not establish that one of skill would have any reasonable expectation that the currently claimed peptides are immunogenic.*

The Examiner states that "it would have been obvious for those skilled in the art intending to developing [sic] a HPV-8 vaccine to start from the E2 protein of HPV-8 since the E2 protein of HPV-16 is a strong immunogenic protein as taught by Konya." (Office Action, page 4).

However, even if one of skill were to combine Konya, Boeckle and Kubo, one of skill would not have a reasonable expectation of success. Konya teaches that while the proliferative T-cell responses against the HPV-16 E1 and E2 proteins had been described, "only a few cervical patients with the relevant HLA haplotypes . . . showed a memory CTL response against an E7 epitope of HPV-16" and that not all epitopes of E1 and E2 were immunogenic. (Konya, 2616, col. 1, lines 16-19 and 2618, col. 1). Moreover, as explained above, E2 and PBF (the protein of which peptides of the instant invention are fragments) *have very little or no structural similarity,* and Konya teaches that "even a single residue change can be deleterious for CTL recognition." (Konya 2618, col. 2, lines 34-35). Furthermore, PBF is a protein endogenous to the human host, not a viral protein. Thus, it is not a foregone conclusion that the PBF protein would be immunogenic based on the disclosures of Konya, Boeckle and Kubo.

In addition, the Examiner states that "any work associated with the design and search [of the HPV-8 E2 protein and the method of screening for CTL-epitopes] would be considered routine experimentation." (Office Action, page 4). However, the Examiner is basing her conclusion on the fact that the E2 protein of HPV-16 was found to be immunogenic. The Examiner has plainly missed that the invention relates to a second protein binding to the E2 protein binding site (such as PBF). The Examiner seems to have misunderstood exactly what it is that Applicants are claiming.

For all of the above reasons, one of skill would not have had any reasonable expectation that the peptides of the invention are immunogenic based upon the cited references. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness. Applicants request that the rejection be withdrawn.

d. Substance of Interview - the Examiner mistakenly relies upon a presumption of similarity of biochemical function based only upon a similarity of binding activity

An interview with the Examiner was held on June 17, 2009. Applicants thank the Examiner for speaking with their representatives. No agreement was reached, but Applicants' representatives thank the Examiner for extending to them the courtesy of an Interview. Applicants would like to address the substance of the interview.

In that interview, the Examiner took a position that, because epitopes of HPV15-E2 are known to be useful to treat cancer, therefore, epitopes of HPV8-E2 would be useful to treat cancer, and therefore a protein, *e.g.*, PBF, which binds to the same region of the HPV genome as HPV8-E2, must be useful to treat cancer *and* must raise a cytotoxic T-cell response as the method of treating cancer. The Examiner concludes that this syllogism establishes an expectation of success in making the present invention.

The Examiner seems to be improperly relying on an inherency theory. Furthermore, her assertion simply does not logically follow from her premises. That is, the Examiner's position is

that, because HPV8-E2 and PBF bind to the same nucleotide sequence in HPV, they necessarily have the same biochemical activities and same disease related properties.

However, there is no justification for this position whatsoever. For example, it is well-known in the art that both transcriptional repressors and transcriptional promoters, *i.e.* proteins, have opposite biochemical activities, can bind to the same promoter site. *See,* for example, the Sekido abstract (*Genes to Cells* 2:771-783 (1997)), copy attached. This abstract describes that the repressor protein deltaEF1 acts in part by competing with a transcriptional activator for the same binding site.

Since the Examiner's rationale for asserting obviousness of the present invention is logically flawed, it cannot serve to establish *prima facie* obviousness of the present invention and the instant rejection must be withdrawn for this further reason as well.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell Reg. No. 36,623 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

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Attachments: Sequence Alignment between HPV8-E2 and PBF
Stubenrauch et al.
Sekido et al. abstract
Boon (1993)

DRN/MHE/cjd